

a₁
the group consisting of TRP (tryptophan), KYN (kynurenine), 3HOKYN (3-hydroxykynurenine), AA (anthranilic acid), 3HOAA (3-hydroxyanthranilic acid), KA (kynurenic acid) and QUIN (quinolinic acid).

34/3. The method of claim 2, wherein a mathematical function of said concentrations of said pair of metabolites is measured.

35/4. The method of claim 2, wherein a concentration of each of substantially all of said kynurenine metabolites is measured.

64/5. The method of claim 2, wherein step (c) comprises the step of determining a mathematical function of said at least one neuroprotective metabolite and said at least one neurotoxic metabolite, and the method further comprises the steps of:

- Rule 1.124
- (d) measuring a concentration of an AED (anti-epileptic drug) in the sample of the subject; and
 - (e) correlating said concentration of said AED with said mathematical function of said neurotoxic metabolite and said neuroprotective metabolite to determine an efficacy of treatment with said AED.

37/6. The method of claim 5, further comprising the step of:

- (f) adjusting a treatment regimen for said AED in the subject according to said mathematical function of said metabolites.

51/7. A method for detecting a predisposition to epilepsy in a subject, the subject being substantially free of signs and symptoms of clinical epilepsy, the method comprising the steps of:

- (a) obtaining a sample from the subject;
- (b) measuring a concentration of at least two kynurenine metabolites, including at least one neuroprotective metabolite and at least one neurotoxic metabolite, in the sample; and
- (c) comparing said concentration of said at least two kynurenine metabolites in the

21
sample to a range of values of said concentrations of said at least two kynurenine metabolites for normal individuals, such that if said concentrations of said at least two kynurenine metabolites in the sample lie outside of said range of values for normal individuals, the predisposition to epilepsy in the subject is detected.

59/ 8. A method for determining an efficacy of treatment with an AED (anti-epileptic drug) in a subject, comprising the steps of:

- (a) obtaining a sample from the subject;
- (b) measuring a concentration of at least two kynurenine metabolites in the sample; and
- (c) comparing said concentrations to an expected range of values for individuals with diagnosed epilepsy substantially controlled by treatment with an AED, such that the efficacy of treatment with the AED in the subject is determined.

60/ The method of claim 8, wherein step (c) comprises the step of determining a mathematical function of said at least one neuroprotective metabolite and said at least one neurotoxic metabolite, and the method further comprises the step of:

- (d) comparing said mathematical function to an expected range of values for individuals with diagnosed epilepsy substantially controlled by treatment with an AED, such that the efficacy of treatment with the AED in the subject is determined.

61/ 10. The method of claim 9, further comprising the steps of:

- (e) measuring a concentration of the AED in the sample of the subject; and
- (f) correlating said concentration of the AED with said mathematical function to determine the efficacy of treatment with the AED in the subject.

62/ 11. The method of claim 10, further comprising the step of:

- (g) adjusting a treatment regimen for the AED in the subject according to the mathematical functions of said metabolites.

a1 63/ 12. A diagnostic system for diagnosing of epilepsy or predisposition to epilepsy in a subject, comprising:

- Rule 1.124
- (a) a sample taken from the subject; and
 - (b) a measurer for measuring a concentration of at least two kynurenine metabolites, including at least one neuroprotective metabolite and at least one neurotoxic metabolite, in said sample; and
 - (c) a correlator for correlating said concentrations of said at least two kynurenine metabolites in said sample with a range of values for said ratios of said at least two metabolites for normal individuals, such that if said mathematical functions of said at least two metabolites in said sample lie outside of said range of values for normal individuals, diagnosis of epilepsy or predisposition to epilepsy in the subject is detected.

64/ 13. A method for quantitatively diagnosing a predisposition to epilepsy in a subject, the method comprising the steps of:

- 65/
- (a) obtaining a sample from the subject;
 - (b) measuring a concentration of at least two kynurenine metabolites in the sample, including at least one neurotoxic metabolite and at least one neuroprotective metabolite, to form a pattern and a mathematical function of said at least two kynurenine metabolites for the subject; and
 - (c) comparing said pattern and said mathematical function in the sample to a pattern and a mathematical function of values of said at least two kynurenine metabolites for individuals with non-treated epilepsy, a predisposition to epilepsy is diagnosed in the subject, said predisposition being quantitatively determined according to said mathematical function.

65/ 14. A method for evaluating an efficacy of an AED (anti-epileptic drug) in a subject comprising the steps of;

- (a) obtaining a first sample from the subject;
- (b) measuring a first concentration of at least two kynurenine metabolites in the

a1

sample including at least one neurotoxic metabolite and at least one neuroprotective metabolite, to form a pattern and a mathematical function of said at least two kynurenine metabolites for the subject;

- (c) administering the AED to the subject;
- (d) obtaining a second sample from the subject;
- (e) measuring a second concentration of at least two kynurenine metabolites in the sample including at least one neurotoxic metabolite and at least one neuroprotective metabolite, to form a pattern and a mathematical function of said at least two kynurenine metabolites for the subject; and
- (f) comparing said first pattern and mathematical function to said second pattern and mathematical function, such that the efficacy of treatment with the AED in the subject is determined in accordance with an acquired balance of kynurenine metabolites.

15. A quantitative method for detecting a predisposition to epilepsy in a subject, the subject being substantially free of signs and symptoms of clinical epilepsy, the method comprising the steps of:

- (a) obtaining a sample from the subject;
- (b) measuring a concentration of at least two kynurenine metabolites, including at least one neuroprotective metabolite and at least one neurotoxic metabolite, in the sample; and
- (c) comparing said concentration of said at least two kynurenine metabolites in the sample to a range of values of said concentrations of said at least two kynurenine metabolites for normal individuals, such that if said concentrations of said at least two kynurenine metabolites in the sample lie outside of said range of values for normal individuals, the predisposition to epilepsy in the subject is detected.

Respectfully Submitted

Mark M. Friedman
Attorney for Applicant
Registration No. 33,883

Date: 13 November, 2000

67. 1. (new) A method for diagnosis comprising:

- a) obtaining a sample from a subject;
- b) measuring a concentration of at least two kynurenine metabolites in said sample;
- c) comparing said concentrations of said at least two kynurenine metabolites to corresponding reference concentrations of said at least two kynurenine metabolites; and
- d) diagnosing a medical condition based on results of said comparing.

68. 2. (new) The method of claim ⁶⁷1, wherein said at least two metabolites are selected from a group consisting of neuroprotective metabolites and neurotoxic metabolites.

69. 3. (new) The method of claim ⁶⁷2, wherein said group consists of TRP (tryptophan), KYN (kynurenine), 3HOKYN (3-hydroxykynurenine), AA (anthranilic acid), 3HOAA (3-hydroxyanthranilic acid), KA (kynurenic acid) and QUIN (quinolinic acid).

70. 4. (new) The method of claim 2 wherein a first metabolite selected is a neuroprotective metabolite and a second metabolite selected is a neurotoxic metabolite.

71. 5. (new) The method of claim 4 wherein said first metabolite is KA (kynurenic acid) and said second metabolite is 3HOAA (3-hydroxyanthranilic acid).

72. 6. (new) The method of claim 4 wherein said first metabolite is AA (anthranilic acid) and said second metabolite is 3HOAA (3-hydroxyanthranilic acid).

73. 7. (new) The method of claim 4 wherein said first metabolite is KA (kynurenic acid) and said second metabolite is QUIN (quinolinic acid).

74. 8. (new) The method of claim 1 wherein said medical condition is related to epilepsy.

75. 9. (new) The method of claim 8 wherein said medical condition is epilepsy.

Application Number 09/449,748

3

Rule
1.126 70 75 10. (new) The method of claim 8 wherein said medical condition is a predisposition to epilepsy.

77 76 11. (new) The method of claim 10 wherein said subject is substantially free of clinical manifestations indicative of epilepsy.

16 77 12. (new) The method of claim 1 wherein said corresponding reference concentrations are metabolite concentrations of an individual without said medical condition.

79 78 13. (new) The method of claim 1 wherein said corresponding reference concentrations are metabolite concentrations of an individual with said medical condition.

cr2 79 14. (new) The method of claim 1 wherein said corresponding reference concentrations are metabolite concentrations of an epileptic.

B 80 15. (new) The method of claim 1 wherein said comparing comprises

- i) determining a first ratio, being a ratio of two of said determined metabolite concentrations;
- ii) determining a second ratio, being a ratio of two of said corresponding reference concentrations; and
- iii) comparing said first ratio to said second ratio.

81 16. (new) The method of claim 1 wherein said comparing comprises

- i) defining a function, said function being dependent on metabolite concentrations;
- ii) determining a first value, said first value determined by a value of said function at said determined metabolite concentrations;
- iii) determining a second value, said second value determined by a value of said function at said corresponding reference concentrations; and
- iv) comparing said first value to said second value.

Application Number 09/449,748

83 ~~82~~ 17. (new) The method of claim 16 wherein said function is selected from the group comprising:

Rule 1.104
$$([KA][3HOKYN])/([KYN][3HOAA])$$

$$([KA] + [AA]) / [3HOAA];$$
$$[3HOAA] / [3HOKYN];$$
$$[KA] / ([3HOAA][TRP]); \text{ and}$$
$$([KA] + [AA]) / ([3HOAA][TRP]).$$

84 ~~83~~ 19. (new) The method of claim 1, further comprising:

e) determining an amount of an anti-epileptic drug in the subject; and wherein said diagnosing of said medical condition is further based on said determined amount of said anti-epileptic drug.

CRX
84 ~~83~~ 20. (new) The method of claim 19 wherein said determining said amount of said AED comprises measuring a concentration of said AED in said sample.

B
85 ~~84~~ 21. (new) The method of claim 19 wherein said determining said amount of said AED comprises noting a dosage of said AED given to said subject.

86 ~~85~~ 22. (new) The method of claim 19 wherein said medical condition is an individual reaction to an anti-epileptic drug.

87 ~~86~~ 23. (new) The method of claim 22, further comprising:

(f) adjusting a treatment regimen of said subject based on said diagnosing of said medical condition.

Application Number 09/449,748

14 88 / 24. (new) A system for diagnosis comprising:

a) a sample taken from a subject; and

b) a device configured to:

i) measure a concentration of at least two kynurenine metabolites in said sample; and

ii) compare said concentrations of said at least two kynurenine metabolites to corresponding reference concentrations of said at least two kynurenine metabolites.

CR 24 90 89 / 25. (new) The system of claim 24 wherein at least one of said at least two kynurenine metabolites is a neurotoxic metabolite and at least one of said at least two kynurenine metabolites is a neuroprotective metabolite.

B₁ 90 / 26. (new) The system of claim 24 wherein said device is configured to compare said concentrations by:

a. determining a first ratio, being a ratio of said measured metabolite concentrations;

b. determining a second ratio, being a ratio of said corresponding reference concentrations; and

c. comparing said first ratio to said second ratio.

90 91 / 27. (new) The system of claim 24 wherein said device is further configured to:

iii) display a possible diagnosis of a medical condition based on results of said comparing.

92 / 28. (new) The method of claim 27 wherein said medical condition is related to epilepsy.